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10/790,224	03/02/2004	Yumi Matsuzaki	US-162	9934
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ACS LLC			ART UNIT	
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SUITE B			1656	
ALEXANDRIA, VA 22314			DATE MAILED: 08/11/2005	

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/790,224

Applicant(s)

MATSUZAKI ET AL.

Examiner

Lindsay Odell

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 5-7 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4, 8 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 18 March 2005
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: See Continuation Sheet

Continuation of Attachment(s) 6). Other: Alignment of SEQ ID NO: 20 in Amino Acid Database.

## **DETAILED ACTION**

### ***Application Status***

1. In response to the previous Office action, a written restriction requirement (mailed on April 21, 2005), Applicants filed a response received on May 13, 2005. Claims 1-10 are pending in this instant Office action.

### ***Election***

2. Applicant's election with traverse of Group I, Claims 3-4, drawn to a coryneform bacteria wherein glutamine synthetase activity is enhanced by mutating the adenylation site of glutamine synthetase, in the reply filed on May 13, 2005 is acknowledged. The traversal is on the grounds(s) that no undue burden would be placed on the Examiner to examine all the pending claims together and the searches are coextensive. This is not found persuasive because the Groups of claims are distinct for the reasons previously cited, and the searches are not co-extensive because the groups are classified differently and the searches in textual databases are different; thus, the Groups of claims would be burdensome to be searched together.

The requirement is still deemed proper, and is, therefore, made FINAL. Claims 1-10 are pending in the instant Office action. Claims 5-7 and 10 are withdrawn as non-elected inventions. Claims 1-2 and 8-9 are linking claims that link Groups I-IV. As previously noted, the restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1-2 and 8-9. Claims 1-4 and 8-9, to the extent that they are drawn to the elected subject matter, are examined herein.

***Priority***

3. The instant application is granted the benefit of priority for the foreign application 2003-56129 filed in Japan on March 3, 2003 as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d) or (f), which papers have been placed of record in the file. Said papers are not in English and no translation has been filed.

***Information Disclosure Statement***

4. The information disclosure statement (IDS) filed March 18, 2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following reference was not considered for the reasons described below:

- a) The citation of the European Search Report is improper because the corresponding European application is not referenced, nor is a copy provided.

All other documents in said Information Disclosure Statement were considered as noted by the examiner's initials in the attached copy.

5. The lists of related cases submitted on March 18, 2005 have been received and placed in the file.

***Compliance with Sequence Rules***

6. The sequence listing, filed in computer readable form (CRF) and paper copy on August 27, 2004 has been received and entered.

***Objections to the Specification***

7. The specification is objected to because the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Coryneform bacteria having L-arginine or L-lysine producing ability and enhanced glutamine synthetase activity---.

8. The disclosure is objected to because of the following informalities: the numbering of the Examples in the "Examples" section of the disclosure (pages 27-37) is improper because the first two examples are both numbered Example 1 (see page 27 and 29) and the consecutive examples are numbered 2-3. The Examples should be renumbered to reflect the total number of examples (i.e. 1-4). Appropriate correction is required.

***Claim Objections***

9. Claim 3 and 4 are objected to because of they contain non-elected subject matter. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

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invention. The term "*the* adenylylation site of glutamine synthetase" is unclear as to the metes and bounds it imparts on the claimed subject matter. It is unclear exactly which adenylylation site of a glutamine synthetase be mutated. Type I glutamine synthetase from *Corynebacterium glutamicum* (encoded by *glnA*) has only one adenylylation site; however, the adenylylation site referred to in the instant claim is from *any* glutamine synthetase from *any* coryneform bacteria. It is unclear that all glutamine synthetases in coryneform bacteria have an adenylylation site, or that they have only one adenylylation site. For example does *Corynebacterium glutamicum* type II glutamine synthetase (encoded by *glnA2*) have one or more adenylylation sites? If a glutamine synthetase has more than one adenylylation site, or no adenylylation site, which residue should be mutated? Clarification is required.

11. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "wherein said adenylylation site comprises position 405 of SEQ ID NO: 20" is unclear as to the metes and bounds it imparts on the claimed subject matter. The adenylylation site referred is the glutamine synthetase from *any* coryneform bacteria; however SEQ ID NO: 20 describes the sequence of a glutamine synthetase from *Brevibacterium lactofermentum* (also called *Corynebacterium glutamicum*). It is unclear if Applicant means to claim a coryneform bacteria wherein the glutamine synthetase modified is described by SEQ ID NO: 20 and the adenylylation site is at position 405; or if Applicant means to claim a coryneform bacteria that has an adenylylation site that corresponds to position 405 of the glutamine synthetase described by SEQ ID NO: 20. If Applicant means to claim the latter, it is unclear how

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to determine which residue corresponds to the adenylylation site at position 405 in SEQ ID NO:

20. Clarification is required.

12. Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "an arginine repressor" is unclear as to the metes and bounds it imparts on the claimed subject matter. It is unclear exactly which arginine repressor be modified or disrupted. For claim 8, must the arginine repressor that is modified be endogenous (i.e., from a particular coryneform bacteria), or can it be from any organism? For claim 8, must an arginine repressor be a protein, or can it be another kind of molecule? If the arginine repressor is a protein (as required by claim 9), the nature of the protein is wholly unclear. Is the protein a repressor of arginine biosynthesis, arginine metabolism, arginine export or arginine import? What must a molecule look like to be considered an arginine repressor? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-4 and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to



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coryneform bacteria that cause an accumulation of L-arginine or L-lysine in media when cultured and that are modified so that glutamine synthetase activity is enhanced compared to wild-type coryneform bacteria (claim 1, see page 6 of specification), optionally modified so that an arginine repressor does not function normally (claim 8), optionally modified so that a gene encoding an arginine repressor is disrupted (claim 9), or optionally which have a modification that results in adenylation of glutamine synthetase being reduced or eliminated (claim 2), wherein the modification is a mutation of the adenylation site of glutamine synthetase (claim 3), wherein the adenylation site corresponds to position 405 of SEQ ID NO: 20 and is a replacement of wild-type tyrosine with another amino acid (claim 4). While the function and structure of species of said genera of coryneform bacteria are disclosed in the specification, the structure of a representative number of species is not adequately described, nor are the common functional or structural characteristics of species that describe said genera identified.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at \*23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical

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characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

On pages 27-34 of the instant specification, a *Brevibacterium lactofermentum* strain is described (2256 or (ATCC13869)) that contains a chromosomal mutation in the *glnA* gene encoding glutamine synthetase (described by SEQ ID NO: 20) that results in replacement of the L-tyrosine at position 405, the adenylation site, with an L-phenylalanine. This strain also has a disruption of the *argR* gene (SEQ ID NO: 15) encoding the arginine repressor described by SEQ ID NO: 16. The instant *B. lactofermentum* strain causes an accumulation of arginine and lysine in media when cultured and has an increase in glutamine synthetase activity compared to the unmodified strain (see page 34). Applicants have described structural features of the genus relating to *Brevibacterium lactofermentum* having L-arginine or L-lysine producing ability in which SEQ ID NO: 20 is modified at position 405 and/or in which SEQ ID NO: 15 is disrupted; however, these structural limitations are not included in the claims. The structural limitation in claim 4 is unclear because it is not required that the glutamine synthetase be that of *Brevibacterium lactofermentum* (SEQ ID NO: 20) (see 112, 2nd paragraph rejection). While coryneform bacteria that cause an accumulation of L-arginine or L-lysine are known in the art, the common structural characteristics of the species in the genus of L-arginine and L-lysine coryneform bacteria that correlate to a functional limitation are lacking. Likewise, while the structure of certain glutamine synthetase genes and arginine repressor genes are known in the art, the common structural characteristics of species in the genera of glutamine synthetase and arginine repressor genes that correlate to a functional limitation are lacking. In view of the prior

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art, one of skill in the art would be unable to predict the structure of *all* the other members of these genera by virtue of the instant disclosure. Therefore, claims drawn to the instant genus of polypeptides are not adequately described.

14. Claims 1-4 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for *B. lactofermentum* in which activity of the glutamine synthetase described by SEQ ID NO: 20 is enhanced by mutating the adenylylation site at position 405 and in which the gene encoding the arginine repressor described by SEQ ID NO: 15 is disrupted, does not reasonably provide enablement for genera of coryneform bacteria having L-arginine or L-lysine production ability in which glutamine synthetase activity is enhanced (claims 1-4), and in which an arginine repressor is optionally modified (claims 8-9) encompassed by the scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To produce the products necessary to practice the claimed methods would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

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needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches the *Brevibacterium lactofermentum* strain described above that contains a particular chromosomal mutation in the *glnA* gene encoding glutamine synthetase (described by SEQ ID NO: 20) and disruption of the *argR* gene (SEQ ID NO: 15) encoding the arginine repressor described by SEQ ID NO: 16. This strain has L-arginine and L-lysine producing ability. The specification also teaches *Brevibacterium lactofermentum* strains that have disruption of the *glnE* gene described by SEQ ID NO: 17 or disruption of the gene *amtR* (described by SEQ ID NO: 21), which have increased glutamine synthetase activity and L-arginine and L-lysine producing ability.

However, the specification contains no working examples of coryneform bacteria in which the activity of glutamine synthetase is enhanced other than coryneform bacteria in which the activity of the glutamine synthetase described by SEQ ID NO: 20 is enhanced by particular methods. While the art contains guidance for increasing the activity of the glutamine synthetase described by SEQ ID NO: 20 by over-expressing it in coryneform bacteria, it provides little guidance for over-expressing or otherwise enhancing the activity of glutamine synthetases with

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distinct structures from other species. The state of the prior art is such that few other **coryneform** glutamine synthetases are known; thus, the predictability of making modifications to the glutamine synthetases that would eliminate adenylation is low. In addition, the effect of mutating tyrosine 405 of the glutamine synthetase described by SEQ ID NO: 20 to a residue other than phenylalanine is unknown; the function of a polypeptide is related to its structure, and with a deviation from the known sequence, maintaining function becomes unpredictable.

In addition, the nature of the invention is such that regulation of the activity glutamine synthetase is complex, involving many environmental factors and enzymes (Rhee *et al*, see PTO-892). Without knowing the exact structure and role that these factors and enzymes play in regulating glutamine synthetase activity in coryneform bacteria, the predictability of enhancing glutamine synthetase activity is low. To make all of the modifications that increase glutamine synthetase activity or that result in adenylation of glutamine synthetase being reduced or eliminated encompassed by the scope of the claims would require undue experimentation.

Lastly, the specification contains no working examples of coryneform bacteria modified so that an arginine repressor does not function normally other than those that have a disrupted arginine repressor gene described by SEQ ID NO: 15. While the art and the specification provide guidance for finding and identifying coryneform bacteria that are modified so that an arginine repressor does not function normally, these methods do not enable one of skill in the art to make all, or a relevant portion of, the coryneform bacteria within the scope of the claims. The ability to find a coryneform bacterium that is modified within the scope of the instant claims is not equivalent to the ability to make a mutant strain as required by the statute (i.e., "make and use"). The nature of the invention is such that the DNA encodes a functional protein, an

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arginine repressor, whose function is unknown (see 112 2nd paragraph rejection); and without knowing the exact function or structure, the predictability of functionality of modification is extremely low. Thus, while some arginine repressors are known in the art, modifying their function would be wholly unpredictable.

In conclusion, to make all the coryneform bacteria included in the breadth of the claims would require undue experimentation. Therefore, the instant claims are not enabled to the full extent of their scope.

*Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15. Claims 1-4 and 8-9 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claims, as written, does not sufficiently distinguish over bacteria as they naturally exist because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Although bacteria can be modified in the laboratory, bacteria exist in nature that can be considered to be modified because of naturally occurring mutations. It is not clear that the modified bacteria referred to in the claims are only those isolated or engineered in the laboratory. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. The claim should be amended to indicate the hand of the inventor, e.g. by

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insertion of “isolated”, as taught on pages 27-37 of the specification. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206, USPQ 193 (1980).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Loos *et al.* (see PTO-892) as evidenced by Nakayama *et al.* (US Pat 3708395, see PTO-892). The instant claim is drawn to a coryneform bacterium which has an L-lysine producing ability (an ability to cause accumulation of L-lysine in a medium when the bacteria is cultured in the medium) and which is modified so that glutamine synthetase activity is enhanced as compared to wild-type coryneform bacteria.

Loos *et al.* teach a *Corynebacterium glutamicum* strain (ATCC 21253) that has increased gene expression of glutamine synthetase during L-lysine production (see Table 1). In the broadest reasonable interpretation of the claims, an increase in the expression of glutamine synthetase can be considered an increase in glutamine synthetase activity. The strain used by Loos *et al.* secretes L-lysine into the medium (page 2310, column 2); thus it has L-lysine producing ability, as defined by Applicant. The strain used by Loos *et al.* was also modified to increase L-lysine production, as evidenced by Nakayama *et al.* (Column 3, Experiment 1). This modification causes the instant strain to use glutamine, which is produced by glutamine synthetase, as a primary nitrogen source during L-lysine production (Loos *et al.*, page 2317,

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column 1). Thus, it is reasonable to assert that a modification, compared to wild-type coryneform bacteria, is responsible for the increase glutamine synthetase activity in the strain taught by Loos *et al.* Thus, the strain taught by Loos *et al.* has L-lysine producing ability and has been modified to increase glutamine synthetase activity compared to wild-type coryneform bacteria.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 2-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Loos *et al.* in further view of Jakoby *et al.* and Arcondeguy *et al.* The instant claims are drawn to coryneform bacteria that have an L-lysine producing ability (an ability to cause accumulation of L-lysine in a medium when the bacteria is cultured in the medium), and that are modified to reduce or eliminate adenylation of glutamine synthetase (claim 2), wherein the modification is mutation of the adenylation site of glutamine synthetase (claim 3), wherein said adenylation site comprises position 405 of SEQ ID NO: 20 and the wild-type tyrosine is replaced with another amino acid (claim 4).

Loos *et al.* teach a strain of *Corynebacterium glutamicum* that has L-lysine producing ability and has been modified to increase glutamine synthetase activity compared to wild-type



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coryneform bacteria (see 35 U.S.C. 102 (b) rejection above). Loos *et al.* do not teach mutating the adenylation site of glutamine synthetase to increase its activity.

Arcondeguy *et al.* teach that replacement of the tyrosine that is adenylylated in *R. meliloti* glutamine synthetase with phenylalanine, a residue that cannot be adenylylated, results increased activity of the enzyme (see pages 37-38, section 3.4). Thus, Arcondeguy *et al.* teach that inhibition of adenylation of glutamine synthetase increases glutamine synthetase activity in *R. meliloti* (but not coryneform bacteria).

Jakoby *et al.* teach that the adenylation site for *Corynebacterium glutamicum* glutamine synthetase I (encoded by *glnA*) is Tyrosine-405 (see Figure 1). In the broadest reasonable interpretation of the claims, residue Tyrosine-405 of the glutamine synthetase taught by Jakoby *et al.* is position 405 of SEQ ID NO: 20 because it corresponds to position 405 of SEQ ID NO: 20 (see 112, 2nd paragraph rejection and attached alignment). Jakoby *et al.* do not teach that replacing the adenylation site residue (a tyrosine) of *C. glutamicum* glutamine synthetase with another amino acid increases glutamine synthetase activity.

Loos *et al.* teach that *Corynebacterium glutamicum* are useful in the commercial production of lysine and that glutamine synthetase provides the nitrogen source for the L-lysine biosynthesis pathway. Thus, one of skill in the art would also been motivated at the time of the invention to make coryneform bacteria with L-lysine producing ability that have increased glutamine synthetase activity because increasing glutamine synthetase activity would increase the nitrogen source for L-lysine biosynthesis, and, hence, L-lysine production. Furthermore, it would have been obvious at the time of the invention for one of skill in the art to make L-lysine producing *Corynebacterium glutamicum* that have an increased glutamine synthetase activity by

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mutating the adenylation site of glutamine synthetase (a tyrosine) by replacing it with another amino acid residue because of the teachings of Arcondeguy *et al.* and Jakoby *et al.*. Thus, claims 2-4 are unpatentable over Loos *et al.* in further view of Jakoby *et al.* and Arcondeguy *et al.*

***Other Art for Comment/Examiner's Suggestions***

The following are cited to complete the record:

- a) Suga *et al.* (PGPUBS 20020045223 A1, see PTO-892) teach disrupting the *argR* gene encoding an arginine repressor in *Brevibacterium lactofermentum* (*Corynebacterium glutamicum*) to improve L-arginine production. They do not teach enhancing glutamine synthetase activity in the same bacterium.
- b) Wakisaka *et al.* (see PTO-892) teach that *Brevibacterium flavum* is a glutamate producing bacteria and that the activity of *Brevibacterium flavum* (*Corynebacterium glutamicum*) glutamine synthetase is increased by adding ammonium chloride to *B. flavum* cell culture. They do not teach that the instant bacteria cause accumulation of L-arginine or L-lysine in media when cultured.
- c) Rhee *et al.* (see PTO-892) present a detailed analysis of glutamine synthetase from *Escherichia coli*. They teach that glutamine synthetase serves as a source of nitrogen atoms in the biosynthesis of all amino acids. They do not teach coryneform glutamine synthetase, or enhancing glutamine synthetase activity in coryneform bacteria that cause an accumulation of L-arginine or L-lysine in media when cultured.

***Conclusion***

18. Claims 1-4 and 8-9 are rejected for the reasons identified in the numbered sections of the Office action. Applicants must respond to the objections/rejections in each of the numbered sections in the Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lindsay Odell whose telephone number is 571-272-3445. The examiner can normally be reached on M-F, 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lindsay Odell, Ph.D.  
July 27, 2005

  
KATHLEEN M. KERR, PH.D.  
SUPERVISORY PATENT EXAMINER

# SEQUENCE ALIGNMENT of SEQ ID 20 in AMINO ACID DATABASE UniProt

## RESULT 1

Q79VE3

ID Q79VE3 PRELIMINARY; PRT; 477 AA.  
AC Q79VE3; O32354;  
DT 05-JUL-2004 (TrEMBLrel. 27, Created)  
DT 05-JUL-2004 (TrEMBLrel. 27, Last sequence update)  
DT 25-OCT-2004 (TrEMBLrel. 28, Last annotation update)  
DE Glutamine synthase (EC 6.3.1.2) (GLUTAMINE SYNTHETASE I).  
GN Name=glnA; OrderedLocusNames=Cgl2214, cg2429;  
OS Corynebacterium glutamicum (Brevibacterium flavum).  
OC Bacteria; Actinobacteria; Actinobacteridae; Actinomycetales;  
OC Corynebacterineae; Corynebacteriaceae; Corynebacterium.  
OX NCBI\_TaxID=1718;  
RN [1]  
RP SEQUENCE FROM N.A.  
RC STRAIN=ATCC 13032 / DSM 20300 / NCIB 10025 Nakagawa;  
RA Nakagawa S.;  
RT "Complete genomic sequence of Corynebacterium glutamicum ATCC 13032.";  
RL Submitted (MAY-2002) to the EMBL/GenBank/DDBJ databases.  
RN [2]  
RP SEQUENCE FROM N.A.  
RC STRAIN=ATCC 13032 / DSM 20300 / NCIB 10025;  
RX PubMed=12948626; DOI=10.1016/S0168-1656(03)00154-8;  
RA Kalinowski J., Bathe B., Bartels D., Bischoff N., Bott M.,  
RA Burkovski A., Dusch N., Eggeling L., Eikmanns B.J., Gaigalat L.,  
RA Goesmann A., Hartmann M., Huthmacher K., Kraemer R., Linke B.,  
RA McHardy A.C., Meyer F., Moeckel B., Pfefferle W., Puehler A.,  
RA Rey D.A., Rueckert C., Rupp O., Sahm H., Wendisch V.F., Wiegraebe I.,  
RA Tauch A.;  
RT "The complete Corynebacterium glutamicum ATCC 13032 genome sequence  
RT and its impact on the production of L-aspartate-derived amino acids  
RT and vitamins.";  
RL J. Biotechnol. 104:5-25(2003).  
RN [3]  
RP SEQUENCE FROM N.A.  
RC STRAIN=ATCC 13032;  
RX MEDLINE=97442893; PubMed=9297824; DOI=10.1016/S0378-1097(97)00304-2;  
RA Jakoby M., Tesch M., Sahm H., Kraemer R., Burkovski A.;  
RT "Isolation of the Corynebacterium glutamicum glnA gene encoding  
RT glutamine synthetase I.";  
RL FEMS Microbiol. Lett. 154:81-88(1997).  
RN [4]  
RP SEQUENCE FROM N.A.  
RC STRAIN=ATCC 13032;  
RA Jakoby M.J.;  
RL Submitted (MAY-1997) to the EMBL/GenBank/DDBJ databases..  
CC -!- CATALYTIC ACTIVITY: ATP + L-glutamate + NH(3) = ADP + phosphate +  
CC L-glutamine.  
CC -!- SIMILARITY: Belongs to the glutamine synthetase family.  
DR EMBL; AP005281; BAB99607.1; -.  
DR EMBL; BX927154; CAF20554.1; -.  
DR EMBL; Y13221; CAA73664.1; -.  
DR GO; GO:0005737; C:cytoplasm; IEA.  
DR GO; GO:0004356; F:glutamate-ammonia ligase activity; IEA.  
DR GO; GO:0016874; F:ligase activity; IEA.

DR GO; GO:0009399; P:nitrogen fixation; IEA.  
 DR InterPro; IPR004809; GlnA.  
 DR InterPro; IPR008147; Gln\_synt\_beta.  
 DR InterPro; IPR008146; Gln\_synt\_C.  
 DR Pfam; PF00120; Gln-synt\_C; 1.  
 DR Pfam; PF03951; Gln-synt\_N; 1.  
 DR ProDom; PD001057; Gln\_synt\_C; 1.  
 DR TIGRFAMs; TIGR00653; GlnA; 1.  
 DR PROSITE; PS00180; GLNA\_1; 1.  
 DR PROSITE; PS00181; GLNA\_ATP; 1.  
 KW Complete proteome; Ligase.  
 SQ SEQUENCE 477 AA; 53300 MW; 5614B50AC24FF7E5 CRC64;

Query Match 99.8%; Score 2513; DB 2; Length 477;  
 Best Local Similarity 99.6%; Pred. No. 6.6e-187;  
 Matches 475; Conservative 2; Mismatches 0; Indels 0; Gaps 0;

Qy	1	VAFETPEEIVKFIKDENVFVDVRFDTLPGTEQHFSIPAASFADTVEEGLAFDGGSSIRG	60
		:	
Db	1	MAFETPEEIVKFIKDENVFVDVRFDTLPGTEQHFSIPAASFADTIEEGLAFDGGSSIRG	60
Qy	61	FTTIDESDMNLLPDLGTATLDPFRKAKTLNVKFFVHDPFTREAFSRDPRNVARKAEQYLA	120
Db	61	FTTIDESDMNLLPDLGTATLDPFRKAKTLNVKFFVHDPFTREAFSRDPRNVARKAEQYLA	120
Qy	121	STGIADTCNFGAEAEFYLFDSVRYSTEMNSGFYEVDTEEGWWNRGKETNLDGTPNLGAKN	180
Db	121	STGIADTCNFGAEAEFYLFDSVRYSTEMNSGFYEVDTEEGWWNRGKETNLDGTPNLGAKN	180
Qy	181	RVKGGYFPVAPYDQTVDRDDMVRNLAASGFALERFHHEVGGGQQEINYRFNTMLHAADD	240
Db	181	RVKGGYFPVAPYDQTVDRDDMVRNLAASGFALERFHHEVGGGQQEINYRFNTMLHAADD	240
Qy	241	IQTFKYIIKNTARLHGKAATFMPKPLAGDNGSGMHAHQSLWKDGKPLFHDESGYAGLSDI	300
Db	241	IQTFKYIIKNTARLHGKAATFMPKPLAGDNGSGMHAHQSLWKDGKPLFHDESGYAGLSDI	300
Qy	301	ARYYIGGILHHAGAVLAFTNATLNSYHRLVPGFEAPINLVYSQRNRSAAVRIPITGSNPK	360
Db	301	ARYYIGGILHHAGAVLAFTNATLNSYHRLVPGFEAPINLVYSQRNRSAAVRIPITGSNPK	360
Qy	361	AKRIEFRAPDPSGNPYLGFAAMMMAGLDGIKNRIEPHAPVDKDLIELPPEEAASIPQAPT	420
Db	361	AKRIEFRAPDPSGNPYLGFAAMMMAGLDGIKNRIEPHAPVDKDLIELPPEEAASIPQAPT	420
Qy	421	SLEASLKALQEDTDFLTESDVFTEDLIEAYIQYKYDNEISPVRLRPTPQEFELYFDC	477
Db	421	SLEASLKALQEDTDFLTESDVFTEDLIEAYIQYKYDNEISPVRLRPTPQEFELYFDC	477